

L.194.313



PATENT SPECIFICATION

NO DRAWINGS

1.194.313

Inventors: FREDERIC CHARLES SCHAEFER and WILLIAM DOUGLAS ZIMMERMAN

Date of Application (No. 2497/69) and filing Complete Specification: 15 Jan., 1969.

Application made in United States of America (No. 698,122) on 16 Jan., 1968.

Complete Specification Published: 10 June, 1970.

Index at acceptance:—C2 C(20Y, 200, 29Y, 29X, 30Y, 320, 36Y, 364, 746, LA)

International Classification:—C 07 c 123/00

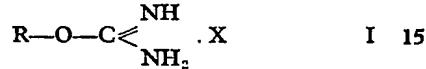
COMPLETE SPECIFICATION

Aqueous process for preparing Pseudoureas and Acid Addition Salts thereof

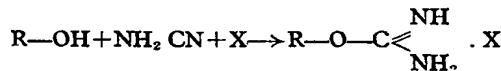
We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a process for preparing pseudourea acid addition salts.

Alkyl pseudourea acid addition salts of the formula:



where R may represent a variety of organic groupings and X is a strong inorganic acid such as hydrochloric or hydrobromic are conventionally prepared by reacting an appropriate organic alcohol with cyanamide in the presence of an acid catalyst X, according to the following reaction:



Prior art teachings have continually emphasized the need for carrying out this reaction under strictly anhydrous conditions in order to avoid the hitherto known rapid hydrolysis of cyanamide to urea which occurs in the presence of an aqueous acidic medium. Such hydrolysis consumes cyanamide on an equimolar basis until all of the water is itself consumed. The teaching of the prior art in this regard is amply demonstrated by reference to Organic Synthesis, collective volume IV, pgs. 645—648 (1963) and to a recent publication by Kawano et al. (*J. Org. Chem. Soc. Japan* 24 (10), pgs. 955—957 (1966)). These two references in calling for anhydrous reactants and anhydrous reaction conditions are merely recent repetitions of what the prior art has urged for years.

The need for anhydrous conditions creates several problems. It necessitates using anhydrous reactants such as, for example, anhydrous cyanamide, anhydrous hydrogen chloride, a frequently used acid catalyst, and anhydrous methanol, a common reactant alcohol. The anhydrous reagents are generally more expensive than their hydrous counter-

parts. Furthermore, the need for strictly anhydrous reaction conditions and the gaseous state of certain anhydrous reactants create many operational problems in carrying out the reaction all of which increase the cost of producing the pseudourea acid addition salts and, consequently, the products prepared from the acid addition salts.

In accordance with the invention there is provided a process for preparing pseudourea acid addition salts of formula I wherein R is derived from a monohydric organic alcohol having at least partial miscibility with water and X is hydrochloric acid or hydrobromic acid, which process comprises bringing into contact in an environment containing substantial amounts of water (a) an acid X, (b) a cyanamide compound, and (c) a monohydric organic alcohol which is at least partially miscible with water. By "substantial amounts of water", it is meant that the reaction mixture contains at least one mole of water for every mole of cyanamide compound, an amount of water ordinarily sufficient to hydrolyze all of the cyanamide compound.

[Price]

According to the process of this invention, good yields of pseudourea acid addition salts are unexpectedly produced despite the presence in the reaction mixture of sufficient water to hydrolyze all of the cyanamide compounds present therein. Surprisingly, the hydrolysis of cyanamide compounds known to occur in an acidic aqueous medium fails to occur in any appreciable amount when the aqueous acidic medium also contains a monohydric organic alcohol even when there is present a huge molar excess of water to cyanamide compound in the reaction mixture. Thus, 80—90% yields of O-methyl pseudourea, for example, are obtainable in reaction mixtures containing as many as 5.8 moles of water per mole of cyanamide. Furthermore, such reaction mixtures contained up to 21% by weight of water, clearly indicating that substantial yields of pseudourea acid addition salts are obtainable without employing the anhydrous reaction conditions previously considered necessary.

Pseudourea yields obtainable by the process of this invention are responsive to variations in the mole ratio of reactant monohydric alcohol to water. This mole ratio, as used herein, refers to the mole ratio in the aqueous phase of the reaction mixture and not necessarily to the mole ratio in the entire reaction mixture. Generally, product yields will increase as the mole ratio of monohydric alcohol to water increases. Suitable results are usually obtainable when mole ratios of 0.8 or higher are employed, with a range of from 0.8 to 3 representing preferred mole ratio values.

An aqueous reaction environment may arise in a variety of ways such as, for example, by the use of aqueous acid solutions or aqueous cyanamide solutions as reactants. The water content of the reaction environment may rise to appreciable levels in the practice of the invention without significant adverse effect on product yields or cyanamide hydrolysis provided the mole ratio of monohydric alcohol to water is properly adjusted to compensate for the water content of the aqueous phase of the reaction mixture.

Since product yields obtained by the process of the invention may be increased by increasing the monohydric alcohol to water mole ratio, it becomes important to retain appreciable amounts of monohydric alcohol in the aqueous phase of the reaction mixture. The more miscible a monohydric alcohol is with water, the greater the mole ratio of monohydric alcohol to water obtainable in the aqueous phase. To this end, it is highly preferred in carrying out the process of this invention to employ monohydric alcohols of high miscibility with water for example allyl alcohol and alkanols containing from one to three carbon atoms, i.e., methanol, ethanol, n-propanol, and isopropanol. Methanol is a particularly

suitable alcohol. When such miscible monohydric alcohols are used, the higher alcohol to water ratios ordinarily conducive to high product yields are readily obtained. Other monohydric alcohols which are less miscible than those mentioned above or which are only partially miscible with water are included within the scope of the invention provided their miscibility with water is sufficient to achieve a suitable monohydric alcohol to water ratio.

Although increasing the mole ratio of monohydric alcohol to water increases the yield of pseudourea acid addition salt, it is preferable from a practical viewpoint to employ the minimal amount of monohydric alcohol required to produce the desired yield of pseudourea acid addition salt. For example, there are limitations on higher ratio values dictated by such considerations as reactor size and alcohol recovery costs. It is difficult to precisely fix a range of operable mole ratios of monohydric alcohol to water since the ratio will vary depending on a variety of factors such as the particular monohydric alcohol employed, the nature of the acid, the desired yield and economic factors. However, as indicated above, best results are generally obtained when monohydric alcohol to water mole ratios of at least 0.8 are employed. To reduce the amount of monohydric alcohol required to maintain the desired ratio value, it is often desirable when adding the acid and cyanamide compound as aqueous solutions to use as highly concentrated solutions as possible.

It is convenient to use at least one mole of cyanamide compound for each mole of acid with a slight excess of cyanamide compound preferred. The excess assures substantially complete usage of the acid in the pseudourea acid addition salt, leaving no acid available to form an acid addition salt of any urea which may be produced in minor amounts from reaction of the cyanamide compound and water. Certain urea acid addition salts, for example urea hydrochloride, are difficult to separate from the pseudourea acid addition salt product and thus the prevention of their formation is an advantage. The excess of cyanamide compound also compensates for minor amounts of the cyanamide compound which may hydrolyze.

Cyanamide, H_2NCN , is the preferred cyanamide compound, but alkali metal or alkaline earth metal salts of cyanamide may also be employed alone or in admixture of two or more. Among such salts which may be employed are the sodium, potassium, or calcium salts such as $CaNCN$, $Ca(HNCN)_2$, $NaHNCN$, or Na_2NCN . When a salt such as $CaNCN$ is employed in place of cyanamide, three moles of hydrochloric acid or hydrobromic acid will be required to provide an equivalent of the acid for reaction with the cyanamide com-

70
7580
85

90

95
100

105

110

115

120

125

130

5 pound since two moles of the acid will be consumed in the neutralization of the cyanamide salt. In similar fashion, two moles of acid will be required when NaHNCN is employed.

10 Reaction pressure and temperature are not considered to be critical. A temperature range of 20°—100°C. is quite suitable with temperatures of 70°—95°C. and atmospheric pressure representing preferred reaction conditions. The pseudourea acid addition salts may be readily converted to the corresponding pseudourea by reaction with a suitable base such as sodium hydroxide, or potassium hydroxide, using known techniques.

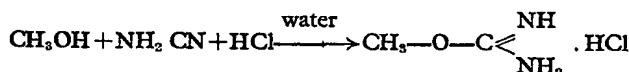
15 Pseudoureas and their acid addition salts

20 are well known intermediates for preparing a host of substituted s-triazines according to the teachings of U.S. Patent Specification No. 3,203,550. The s-triazines are useful as agricultural biocides, surface active compounds, dye intermediates, and pharmaceutical intermediates. The pseudoureas find further utility as intermediates in the preparation of herbicidally active acyl derivatives of pseudoureas according to the teaching of U.S. Patent Specification No. 2,780,535. The pseudoureas are also used as intermediates in the synthesis of certain useful pyrimidines as shown in U.S. Patent Specification No. 2,779,669.

25 The following examples are provided to further illustrate the process of the invention.

35

EXAMPLE 1
Preparation of O-Methyl Pseudourea Hydrochloride



40 Concentrated hydrochloric acid (83.3 ml. 12 N acid; 1.0 mole) is added in 15—30 minutes to a solution of 1.0 mole of 50% aqueous cyanamide (84 g.) in 400 ml. of methanol (9.87 moles). The reaction mixture now contains 20.9% water (5.8 moles). The temperature rises spontaneously to near the boiling point during this addition. The solution is held for an additional 30 minutes at about 70°C.; it is then evaporated essentially to dryness at reduced pressure and at a temperature of below 50°C. The largely crystallized residue is extracted with a small amount of acetone which leaves substantially pure O-methylpseudourea hydrochloride undissolved, melting point 114°C. Yield, 80%.

45 50 55 If the water concentration in the reaction mixture of the preceding example is reduced from 20.9% (5.8 moles) to 13.7% (3.47 moles)

55 by using 100% cyanamide instead of a 50% aqueous cyanamide solution, the average yield is increased to 90%.

EXAMPLES 2 TO 5

60 Following the general procedure of Example 1, a variety of pseudourea acid addition salts are prepared using hydrochloric acid as the catalyst and different alcohols and reaction conditions. Upon completion of the reaction, the solution is evaporated to leave a crude syrup. Aqueous sodium picrate solution is added to the syrup at room temperature with agitation to precipitate the picrate salt of the pseudourea. The salt is then filtered and washed. The results of these Examples are summarized in Table 1. The yield of the pseudourea acid addition salts was calculated from the pseudourea picrates obtained.

20

25

30

60

65

70

TABLE I

Example	Alcohol	Cyanamide	Temp.(°C)	% Water in Reaction Mixture			Moles Cyanamide Moles Water	Product, Hydrochloride Salt of Picrate	Yield (%)	Melting Point* (°C)
				Moles Alcohol	Moles Alcohol	Moles Water				
2	Isopropyl	100% solution	85	13.7	5.2	1.5	O-Isopropyl picrate	38	149—150	
3	Isopropyl	50% aqueous solution	85	21	5.2	1.1	O-Isopropyl picrate	29	149—150	
4	n-Propyl	50% aqueous solution	95	21	5.36	0.93	O-n-Propyl picrate	57	158—160	
5	Allyl	50% aqueous solution	85	20	5.9	1.02	O-Allyl picrate	25	158—160	

* of picrate salt.

WHAT WE CLAIM IS:—

1. A process for preparing a pseudourethane addition salt of the formula:

$$\text{NH}_2 \text{R} \text{O} \text{---} \text{C} \ltreq \text{X} \cdot \text{NH}_2$$

- 5
2. A process according to Claim 1, wherein R is derived from a monohydric organic alcohol having at least partial miscibility with water and X is hydrochloric acid or hydrobromic acid, which process comprises bringing into contact in an environment containing substantial amounts of water: (a) an acid X, as defined above, (b) a cyanamide compound, and (c) a monohydric organic alcohol which is at least partially miscible with water.
- 10
3. A process according to Claim 2, wherein the mole ratio of alcohol to water in the aqueous phase of the reaction mixture is from 0.8 to 3.
- 15
4. A process according to any preceding claim, wherein at least one mole of cyanamide (H_2NCN) is used per mole of acid used.
- 20
5. A process according to any preceding claim, wherein the monohydric organic alcohol is allyl alcohol or an alkanol containing from one to three carbon atoms.
- 25
6. A process according to Claim 5, wherein the alcohol is methanol.
- 30
7. A process according to any preceding claim, wherein the acid is hydrochloric acid.
- 35
8. A process for preparing a pseudourethane addition salt substantially as described in any one of the Examples herein.

9. A pseudourea acid addition salt whenever prepared by a process according to any preceding claim.

10. A pseudourea derived by neutralization with a base of a pseudourea acid addition salt according to any preceding claim.

TREGEAR, THIEMANN & BLEACH,
Chartered Patent Agents,
Melbourne House,
Aldwych, London, W.C.2.
Agents for the Applicants.

Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
which copies may be obtained.